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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,840	01/31/2001	Brian P. Dwyer	257/245	2714

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EXAMINER

TRAN, MY CHAU T

ART UNIT PAPER NUMBER

1639

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/775,840	Applicant(s) DWYER ET AL.	
	Examiner MY-CHAU T. TRAN	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 41,44,49-52,54-57,59,62,64-66,71 and 114-119 is/are pending in the application.
- 4a) Of the above claim(s) 116 and 118 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 114 is/are allowed.
- 6) ☒ Claim(s) 41,44,49-52,54-57,59,62,64-66,71,115,117 and 119 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 31 January 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/31/01</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/22/2005 has been entered.

Application and Claims Status

2. Applicant's amendment and response filed 11/22/2005 is acknowledged and entered. Claim 60 has been cancelled. Claims 41 and 54 have been amended. Claims 115-119 have been added.

3. The amendment filed on 11/04/2004: cancelled claims 1-40, 42, 43, 45-48, 53, 58, 61, 63, 67-70, and 72-113; amended claims 1 and 60; and added claims 114.

4. Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, 71, and 114-119 are pending.

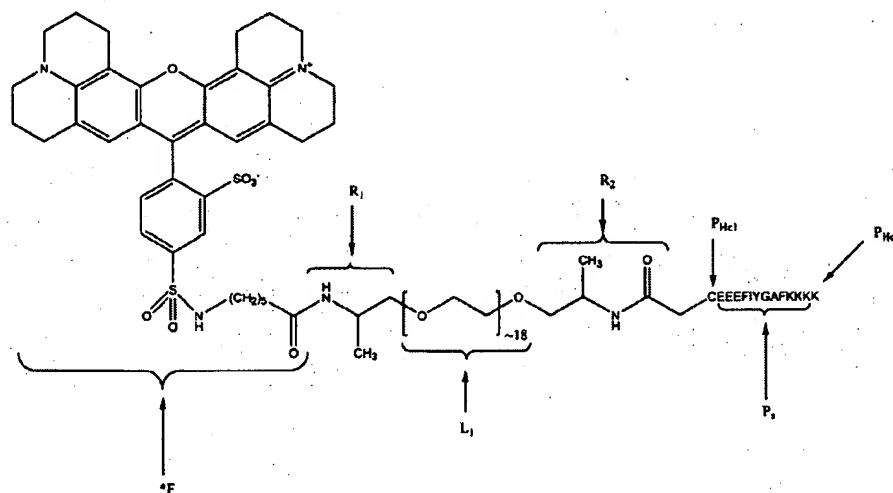
Election/Restrictions

5. The instant species election requirement is still in effect as there is no allowable generic or linking claim. Applicant has elected **without** traverse the following species for the elected

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invention (Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, 71, and 114-119) in the reply filed on 03/12/2004:

For the single specific species of a water-soluble pegylated kinase substrate that would read on the formula of $*F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-(R_3-L_2-R_4-T)_y$, applicant elected the



For the portion $(R_3-L_2-R_4-T)_y$, $y = 0$; therefore $(R_3-L_2-R_4-T)$ is removed.

compound of

Note: the elected species is disclosed in the specification of page 34 (scheme 2), which is Texas Red-Jeffamine₉₀₀-CEEEFIYGAFKKKK [SEQ. ID. NO.: 1]. Furthermore, it is noted that “For the portion $(R_3-L_2-R_4-T)_y$, $y = 0$; therefore $(R_3-L_2-R_4-T)$ is removed” (see Exhibit A of the response filed 03/12/2004). P_{Hc1} is C (cysteine); therefore in the formula of $P_{Hc1} = A_c(A_H)_nA_m$, A_c = cysteine, A_m = covalent bond, and since $n = 0$ A_H is 0. P_{Hc2} is K (lysine); therefore in the formula of $P_{Hc2} = A_m(A_H)_nA_c$, A_c = carboxylic acid moieties since $y = 0$, A_m = covalent bond, and since $n = 0$, A_H is 0. P_S is EEEEFIYGAFKKKK (SEQ. ID. No. 1). Jeffamine₉₀₀ is a polyethylene glycol with the molecular weight of 900.

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6. New claims 116 and 118 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to *a nonelected species*, i.e. the elected species of L₁ is polyethylene glycol with the molecular weight of 900 and L₂ is 'removed', there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 03/12/2004.

7. Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, 71, 114, 115, 117, and 119 are under consideration in this Office Action.

New Rejection(s) – Necessitated by Amendment

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 41, 44, 49-51, 54-57, 71, 115, and 117 are rejected under 35 U.S.C. 102(b) as being anticipated by Belcheva et al. (*Polymeric Materials Science and Engineering*, 1998, 79:471-472) alone or as evidenced by Shimizu et al. (US Patent 4,640,835) regarding the newly added limitation that polyethylene glycol (PEG) having '*the molecular weight of less than about 2000 Daltons*'.

Belcheva et al. disclose the water-soluble fluorescein polymer-peptide conjugates (see e.g. pg. 471, left col., lines 12-25, and 35-39; pg. 472, lines 2-6; pg. 471, fig. 1; pg. 472, fig. 2; pg. 472, Table 1). The peptide (P_s) is 5 amino acids in length (see e.g. pg. 471, left col., lines 17-

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18, and 35-39; pg. 472, lines 2-6). The polymer is polyethylene glycol (PEG) (refers to instant claimed L_1 is polyethylene glycol and instant new claims 115 and 117) with a MW of either 2000 or 5000 (refers to instant claim 57)(see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6). In addition, the new added limitation that the polymer of " L_1 " has '*the molecular weight of less than about 2000 Daltons*' is interpreted to include the '*molecular weight*' of 2000 as supported by the limitation of claim 57. Moreover, it is known in the art that polyethylene glycol (PEG) include lower '*molecular weight*', i.e. less than 2000, as evidence by Shimizu et al., which disclose that polyalkylene glycols having the molecular weight that range from 200 to 20,000 (refers to instant claimed limitation that the polymer of " L_1 " has '*the molecular weight of less than about 2000 Daltons*', and the instant claims 54-56).

The water-soluble fluorescein polymer-peptide conjugates of Belcheva et al., i.e. GRGDY-PEG-fluorescein, read on the claimed substrate member with the general formula of $*F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-(R_3-L_2-R_4-T)_y$, wherein y is 0 (refers to claims 41 and 71), $*F$ is fluorescein (refers to instant claims 49-51), L_1 is polyethylene glycol (PEG), R_1 and R_2 are a covalent bond, P_{Hc1} is a covalent bond, i.e. in the formula of $P_{Hc1} = A_c(A_H)_nA_m$: A_c and A_m = covalent bond, and since $n = 0$, A_H is 0, and P_{Hc2} is a covalent bond with a carboxylic acid moiety, i.e. in the formula of $P_{Hc2} = A_m(A_H)_nA_c$: A_c = carboxylic acid moieties since $y = 0$, A_m = covalent bond, and since $n = 0$, A_H is 0 (see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6).

Therefore, the water-soluble fluorescein polymer-peptide conjugates of Belcheva et al. anticipate the presently claimed library.

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10. Claim 119 is rejected under 35 U.S.C. 102(b) as being anticipated by Belcheva et al. (*Polymeric Materials Science and Engineering*, 1998, 79:471-472) alone or as evidenced by Shimizu et al. (US Patent 4,640,835) regarding the newly added limitation that polyethylene glycol (PEG) having '*the molecular weight of less than about 2000 Daltons*'.

Belcheva et al. disclose the water-soluble fluorescein polymer-peptide conjugates (see e.g. pg. 471, left col., lines 12-25, and 35-39; pg. 472, lines 2-6; pg. 471, fig. 1; pg. 472, fig. 2; pg. 472, Table 1). The peptide (P_s) is 5 amino acids in length (see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6). The polymer is polyethylene glycol (PEG) (refers to instant claimed L_1 is polyethylene glycol) with a MW of either 2000 or 5000 (refers to instant claim 57)(see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6). Moreover, it is known in the art that polyethylene glycol (PEG) include lower '*molecular weight*', i.e. less than 2000, as evidence by Shimizu et al., which disclose that polyalkylene glycols having the molecular weight that range from 200 to 20,000 (refers to instant claimed limitation that the polymer of " L_1 " has '*the molecular weight of less than about 2000 Daltons*').

The water-soluble fluorescein polymer-peptide conjugates of Belcheva et al., i.e. GRGDY-PEG-fluorescein, read on the claimed substrate member with the general formula of $*F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-(R_3-L_2-R_4-T)_y$, wherein y is 0 (refers to claims 41 and 71), $*F$ is fluorescein (refers to instant claims 49-51), L_1 is polyethylene glycol (PEG), R_1 and R_2 are a covalent bond, P_{Hc1} is a covalent bond, i.e. in the formula of $P_{Hc1} = A_c(A_H)_nA_m$: A_c and $A_m =$ covalent bond, and since $n = 0$, A_H is 0, and P_{Hc2} is a covalent bond with a carboxylic acid moiety, i.e. in the formula of $P_{Hc2} = A_m(A_H)_nA_c$: $A_c =$ carboxylic acid moieties since $y = 0$, $A_m =$

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covalent bond, and since $n = 0$, A_H is 0 (see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6).

Therefore, the water-soluble fluorescein polymer-peptide conjugates of Belcheva et al. anticipate the presently claimed library.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belcheva et al. (*Polymeric Materials Science and Engineering*, 1998, 79:471-472), Shimizu et al. (US Patent 4,640,835), and Pomroy et al. (*Biochemical and Biophysical Research Communications*, 1998, 245(2): 618-621).

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Belcheva et al. disclose the water-soluble fluorescein polymer-peptide conjugates (see e.g. pg. 471, left col., lines 12-25, and 35-39; pg. 472, lines 2-6; pg. 471, fig. 1; pg. 472, fig. 2; pg. 472, Table 1). The peptide (P_s) is 5 amino acids in length (see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6). The polymer is polyethylene glycol (PEG) (refers to instant claimed L_1 is polyethylene glycol and instant new claims 115 and 117) with a MW of either 2000 or 5000 (refers to instant claim 57)(see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6). In addition, the new added limitation that the polymer of " L_1 " has '*the molecular weight of less than about 2000 Daltons*' is interpreted to include the '*molecular weight*' of 2000 as supported by the limitation of claim 57. Moreover, it is known in the art that polyethylene glycol (PEG) include lower '*molecular weight*', i.e. less than 2000, as evidence by Shimizu et al., which disclose that polyalkylene glycols having the molecular weight that range from 200 to 20,000 (refers to instant claimed limitation that the polymer of " L_1 " has '*the molecular weight of less than about 2000 Daltons*', and the instant claims 54-56).

The water-soluble fluorescein polymer-peptide conjugates of Belcheva et al., i.e. GRGDY-PEG-fluorescein, read on the claimed substrate member with the general formula of $*F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-(R_3-L_2-R_4-T)_y$, wherein y is 0 (refers to claims 41 and 71), *F is fluorescein (refers to instant claims 49-51), L_1 is polyethylene glycol (PEG), R_1 and R_2 are a covalent bond, P_{Hc1} is a covalent bond, i.e. in the formula of $P_{Hc1} = A_c(A_H)_nA_m$: A_c and $A_m =$ covalent bond, and since $n = 0$, A_H is 0, and P_{Hc2} is a covalent bond with a carboxylic acid moiety, i.e. in the formula of $P_{Hc2} = A_m(A_H)_nA_c$: $A_c =$ carboxylic acid moieties since $y = 0$, $A_m =$ covalent bond, and since $n = 0$, A_H is 0 (see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6).

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The water-soluble fluorescein polymer-peptide conjugates of Belcheva et al. differ from the presently claimed invention by failing to include in the water-soluble fluorescein polymer-peptide conjugates a thioether linkage at R₂ position and the “end” residues (P_{Hc1} and P_{Hc2}) of the peptide has a different net charged.

Pomroy et al. disclose hydrophobic peptides wherein the peptide is coupled to the polyethylene glycol (PEG) by way of the cysteine with a PEG-a-cys reagent (Abstract; pg. 619, left col., line 60 to right col., line 2; fig. 2) (refers to claims 41, 44, and 59). The peptide comprises “end” residues (P_{Hc1} and P_{Hc2}) with different net charged (pg. 619, right col., lines 53-55) (refers to claims 64-66). There are several advantages for attaching Cys side chain to a thiol-reactive PEGs: 1) it can perform under mild reaction conditions allowing for the PEGylation of a target protein under non-denaturing conditions; 2) it is highly targeted; and the disulfide bond between the thiol-reactive Peg and the protein is cleavable with suitable disulfide-reducing agents (pg. 619, right col., lines 29-40).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include in the water-soluble fluorescein polymer-peptide conjugates a thioether linkage at R₂ position and the “end” residues (P_{Hc1} and P_{Hc2}) of the peptide has a different net charged as taught by Pomroy et al. in the library of Belcheva et al. One of ordinary skill in the art would have been motivated to include coupling the peptide to the polyethylene glycol (PEG) by way of the cysteine of the peptidic portion and the “end” residues (P_{Hc1} and P_{Hc2}) of the peptide has a different net charged in the water-soluble fluorescein polymer-peptide conjugates of Belcheva et al. for the advantage of providing a cleavable disulfide bond between the thiol-reactive PEG and the protein (Pomroy: pg. 619, right col., lines 37-40) since both

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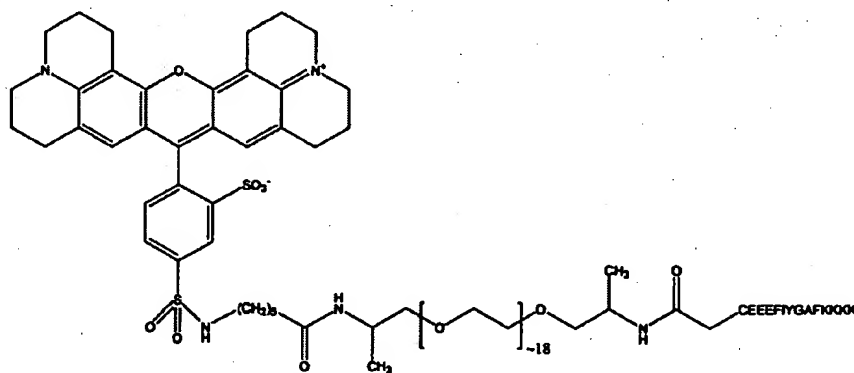
Belcheva et al. and Pomroy et al. disclose composition wherein the peptide is coupled to the polyethylene glycol (Belcheva: pg. 471, left col., lines 12-25, and 35-39; Pomroy: pg. 618, right col., lines 18-33). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Belcheva et al. and Pomroy et al. because Pomroy et al. disclose the success of PEGylation of the peptide using PEG-a-Cys reagent (pg. 620, lines 5-32; fig. 2).

Withdrawn Objection(s) and /or Rejection(s)

14. The rejection of claims 41, 44, 49-52, 64-66, and 71 under 35 USC 102(b) as being anticipated by Burbaum et al. (US Patent 5,876,946) has been withdrawn in light of applicant's amendments of claims 41 and 54.

Allowable Subject Matter

15. Claim 114 is allowable. The following is a statement of reasons for the indication of allowable subject matter: The cited prior art does not teach or fairly suggest the water-soluble peptidic substrate of claim 114 with the formula of



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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 571-272-0810. The examiner can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

My-Chau T. Tran
May 1, 2006

